# Counsyl Autosomal Recessive and X-Linked Classification Criteria (2018)

| Classification | Rules | | Criteria[1] |
|---|---|---|---|
| **Pathogenic** | 1 of A | A | There is significant evidence of association with the variant and disease phenotype.[2] |
| | | | There is significant segregation of the variant in individuals with the disease. |
| | | | The variant fulfills one B criterion and the variant is reported in individuals with disease phenotype; reported cases must be biallelic (autosomal recessive) or hemizygous (X-linked). |
| | | | The variant causes a premature termination codon that is not expected to be targeted by nonsense-mediated mRNA decay; however, literature evidence strongly supports pathogenicity. |
| | | | The amino acid change is the same as a variant classified as pathogenic by Counsyl (excludes variants where the mechanism of pathogenicity is altered splicing). |
| **Likely Pathogenic** | 1 of B and D<br>OR<br>1 of C and D<br>OR<br>1 of E and F and D | B[4] | The variant causes a premature termination codon that is not expected to be targeted by nonsense-mediated mRNA decay; however, literature evidence supports pathogenicity. |
| | | | The variant causes a premature termination codon that is expected to be targeted by nonsense-mediated mRNA decay. |
| | | | The variant is located at IVS +/- 1 or IVS +/- 2 and is expected to disrupt gene function. |
| | | | The variant is an initiation codon variant with no evidence of translation reinitiation downstream and no evidence that an alternative transcript may be used to avoid pathogenicity. |
| | | | The variant leads to a frameshift that disrupts a known active site, a nucleotide or substrate binding site, or a domain known to be essential for protein function. |
| | | | Variant is predicted to result in protein elongation in a gene where stop losses are known to cause disease (pathogenicity is evaluated based on literature evidence). |
| | | | The variant is a large genomic, multi-exon, or single-exon deletion. For in-frame exon deletions, the classification may be downgraded to variant of uncertain significance if the deleted exons are of unknown function or if there are clinically relevant alternative transcripts that are missing the deleted exon(s). |
| | | C | The amino acid change is the same as a variant classified as likely pathogenic by Counsyl (excludes variants where the mechanism of pathogenicity is altered splicing). |
| | | | There is strong evidence of association with the variant and the relevant disease.[2] |
| | | D | The variant is absent or rare in population frequency databases. |

| | | | |
|---|---|---|---|
| | | E | There is suggestive evidence of association with the variant and the relevant disease.[2] [3] |
| | | | There is suggestive segregation of the variant in individuals with the disease. |
| | | F | Functional data showing deficient protein function.[3] |
| **Variant of uncertain significance (VUS)** | 1 of G | G | There is conflicting or insufficient evidence supporting the pathogenicity of the variant. |
| | | | The variant is a gross duplication of unknown structure and function. |
| **Likely Benign** | 1 of H | H | The frequency of the variant is between 1% and 5% in the general population or in a specific subpopulation.[2] |
| | | | The population frequency of the variant is greater than the expected carrier frequency for the disease. |
| | | | The variant is an intronic variant and has been demonstrated by functional studies to have no splicing effect. |
| | | | The variant is silent (synonymous) or is an intronic variant located distant from an intron-exon boundary and there are no reported cases with the variant. |
| | | | There is additional evidence for a benign effect, not accounted for by other criteria. |
| **Benign** | 1 of I | I | The frequency of the variant is >5% in the general population or in a specific subpopulation. |
| | | | The population frequency of the variant is more than 2 times greater than the expected carrier frequency for the disease. |

[1] Certain genes with unique mechanisms of pathogenicity may have specific criteria based on the specific function or characteristics of that gene.

[2] Specific thresholds vary by disease, depending on factors such as prevalence, the number of patients studied in the literature, and multiple hypothesis correction.

[3] Depending on the strength of association with disease phenotype and/or the strength of functional evidence, additional supporting criteria may be required.

[4] Only applies to genes where loss of function is a mechanism of pathogenicity.